BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/124,485	07/29/98	ANSTEY	N 73-97

HM12/0509
GREENLEE WINNER AND SULLIVAN
5370 MANHATTAN CIRCLE
SUITE 201
BOULDER CO 80303

EXAMINER	
GABEL, G	
ART UNIT	PAPER NUMBER
1641	11

DATE MAILED: 05/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/124,485	ANSTEY ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Amendment entry

1. Applicants' amendment and response filed 1/8/01 in Paper No. 10 is acknowledged and has been entered. Claims 1, 3-11, 15-17, 19, 21-22, and 24-26 have been amended. Claims 34-37 have been added. Currently, claims 1-26 and 34-37 are pending and under examination.

Withdrawn Rejections

2. In light of Applicant's amendment and arguments, the rejection of claims 1, 3-17, 19-21, 24-26 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

3. In light of Applicant's argument, the rejection of Claims 1-26 under 35 U.S.C. 112, first paragraph is hereby, withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-6, 9-13, 15, 17-19, 22-23, 26, and newly added claims 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Seguin et al. (The Journal of Experimental Medicine, 1994) for reason of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-7, 9-13, 15, 17-26, and newly added claims 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kremsner et al. (Transactions of the Royal Society of Tropical Medicine and Hygiene, 1996) in view of Liew et al. (Eur Immunol., 1991) for reason of record.

6. Claims 8, 14, and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Seguin et al. or Liew et al. in view of Stamler et al. (Proc. Natl. Acad. Sci. USA, 1992) for reason of record.

Response to Arguments

7. A) Applicant argues that the instant invention cannot be anticipated by Seguin et al. because it only speculates the role of NO in malarial infection which is known but there is no teaching of administering an NO modifying agent for treating or preventing malarial infection. Further Seguin et al. only related to liver stage malaria and not erythrocytic stage malaria. Lastly, Applicant argues that the invention shows that increased levels of NO prevents disease development in non-immunized humans while Seguin et al. only considered the antiparasitic effects rather than the anti-disease effects of the parasitic infection.

In response, Seguin et al., indeed, teach the effects of NO modifying agents to mice in page 355, columns 1-2 wherein the agents (L-arginine analogues) were orally administered via gastric instillation to mice before sporozoite challenge. Results are in Table 1.

In response to Applicant's argument that Seguin et al. only teach liver stage malaria and not erythrocytic stage malaria, it is noted that the feature or limitation in question is not specifically recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Alternatively, Seguin et al. noted that another publication (Taylor-Robinson et al.) has reported the effects of induction of NO by Th1 CD4 cells in blood stage malaria suggesting a teaching of NO effect in erythrocytic stage of malaria in blood cells.

Lastly, Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. In this case, Seguin et al. teach the significance of modifying agents (CD-8 and IFN-λ) in the regulation of induced nitric oxide synthase (iNOS) in liver which contributes to the protective response of mice immunized with irradiated malaria sporozoites (liver stage) of Plasmodium berghei wherein IFN- λ, provided by CD8 T-cells, kills parasites by stimulating or inducing malaria-infected liver cells, hepatocytes, and Kupffer cells to produce increased levels of nitric oxide (NO) for the destruction of hepatocytes or parasites within the cells in both mice and humans (see Abstract).

B) Applicant argues that Kremsner et al. does not teach or suggest administration of NO modifying agent to treat or prevent malaria, especially in blood stage and that NO production contributed to the pathogenicity of malarial disease and thus teaches away from the claimed invention. Applicant also argues that Liew et al. only teach effects of high levels of NO upon activation by IFN-γ and IFN-α cells in killing Leishmania major but does not teach its effects on parasites that cause malaria. Therefore, there is no motivation or suggestion by either references that NO modifying agent can be used to treat malarial infection.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Kremsner et al. teach that high plasma levels of NO in acute phase of Plasmodium falciparum malaria allows accelerated cure; thereby providing evidence and motivation to increase NO levels to effect its protective role in malaria. Kremsner et al. noted that high plasma levels of NO are reportedly toxic in P. falciparum and P. vivax. Kremsner et al. noted that excessive production of NO may be deleterious; thereby suggesting NO production within the network of a directed and regulated modulation of immune response so as to provide a key protective role against malaria infection. Liew et al. is incorporated therewith for teaching that activation of IFN-γ, IFN-α, and lipopolysaccharides (LPS) produce high levels of NO and are efficient in killing intracellular protozoan parasites such as Leishmania major whose leishmanial activity is equivalent to malarial parasitic infection. Therefore, one of ordinary skill in the art at the time of the invention would have been motivated to combine the teaching of Liew with the teaching of Kremsner and modulate effective NO levels for treatment of malarial infection because controlled, regulated, and directed modulation of NO whose

effect is optimally limited by specific dosages, which can otherwise be potentially toxic to the system, is needed to provide acceptable treatment method of malarial infection.

C) Applicant argues that Stamler et al. does not teach or suggest the role of NO in malarial infection and that there is no suggestion that a NO modifying agent can be used to treat malarial infection

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Seguin et al. teach that NO modulating agents kill parasites by stimulating or inducing malaria-infected liver cells, hepatocytes, and Kupffer cells to produce nitric oxide (NO) for the destruction of hepatocytes or parasites within the cells in both mice and humans. Kremsner et al. also teach that high plasma levels of NO in acute phase of Plasmodium falciparum malaria allows accelerated cure; thereby providing evidence and motivation to increase NO levels to effect its protective role in malaria. Stamler et al. has been incorporated therewith for teaching that nitric oxide reacts in the presence of specific protein thiols to form S-nitrosoprotein derivatives and that nitric oxide circulates in the plasma primarily complexed in S-nitrosothiol species. Stamler et al. also teach that pharmacological interventions that modulate nitric oxide generation changes plasma levels of S-nitrosothiols. Therefore, given the teaching that nitric oxide naturally exists in the plasma as being primarily complexed in S-nitrosothiol,

it would have been obvious to one of ordinary skill in the art at the time of the invention to apply the teaching of Seguin and Kremsner of the mechanism involved in modulating NO levels for treatment of malarial infections caused by Plasmodium, so as to be applicable and effective in its state as being complexed in the nitrosothiol species.

8. Applicant's arguments filed 1/8/01 have been fully considered but they are not persuasive. Accordingly, no claims are allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703)

305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

5/7/01

Gailene R. Gabel
Patent Examiner
Art Unit 1641

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
05/07/01